Format: Abstract

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Gene-Based Risk Stratification for Cardiac Disorders in LMNA Mutation Carriers.

Nishiuchi S, Makiyama T, Aiba T, Nakajima K, Hirose S, Kohjitani H, Yamamoto Y, Harita T, Hayano M, Wuriyanghai Y, Chen J, Sasaki K, Yagihara N, Ishikawa T, Onoue K, Murakoshi N, Watanabe I, Ohkubo K, Watanabe H, Ohno S, Doi T, Shizuta S, Minamino T, Saito Y, Oginosawa Y, Nogami A, Aonuma K, Kusano K, Makita N, Shimizu W, Horie M, Kimura T.

Abstract

BACKGROUND: Mutations in *LMNA* (*lamin A/C*), which encodes lamin A and C, typically cause age-dependent cardiac phenotypes, including dilated cardiomyopathy, cardiac conduction disturbance, atrial fibrillation, and malignant ventricular arrhythmias. Although the type of *LMNA* mutations have been reported to be associated with susceptibility to malignant ventricular arrhythmias, the gene-based risk stratification for cardiac complications remains unexplored.

METHODS AND RESULTS: The multicenter cohort included 77 *LMNA* mutation carriers from 45 families; cardiac disorders were retrospectively analyzed. The mean age of patients when they underwent genetic testing was 45±17, and they were followed for a median 49 months. Of the 77 carriers, 71 (92%) were phenotypically affected and showed cardiac conduction disturbance (81%), low left ventricular ejection fraction (<50%; 45%), atrial arrhythmias (58%), and malignant ventricular arrhythmias (26%). During the follow-up period, 9 (12%) died, either from end-stage heart failure (n=7) or suddenly (n=2). Genetic analysis showed truncation mutations in 58 patients from 31 families and missense mutations in 19 patients from 14 families. The onset of cardiac disorders indicated that subjects with truncation mutations had an earlier occurrence of cardiac conduction disturbance and low left ventricular ejection fraction, than those with missense mutations. In addition, the truncation mutation was found to be a risk factor for the early onset of cardiac conduction disturbance and the occurrence of atrial arrhythmias and low left ventricular ejection fraction, as estimated using multivariable analyses.

CONCLUSIONS: The truncation mutations were associated with manifestation of cardiac phenotypes in *LMNA*-related cardiomyopathy, suggesting that genetic analysis might be useful for diagnosis and risk stratification.

KEYWORDS: arrhythmia; cardiomyopathies; death, sudden, cardiac; heart failure; lamin type A; mutation; prognosis

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